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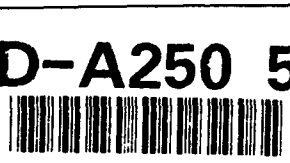

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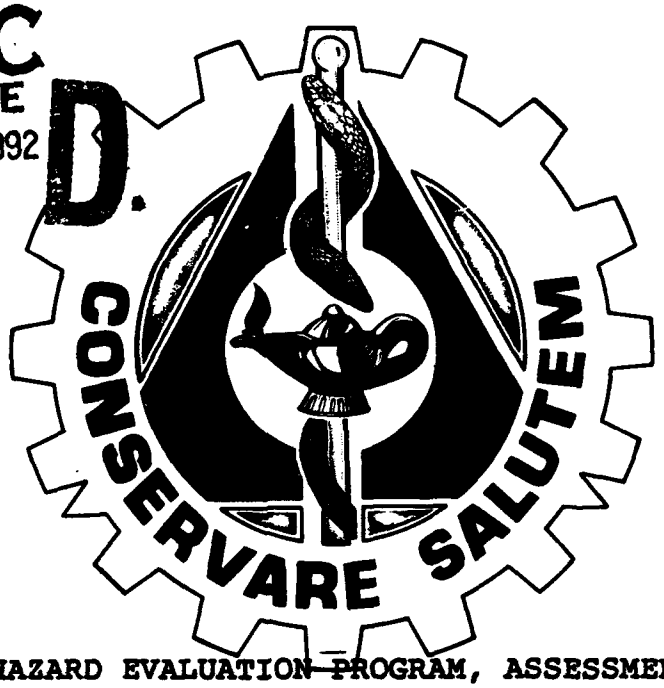

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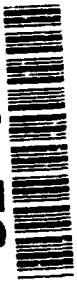

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USAEHA

TOPICAL HAZARD EVALUATION PROGRAM, ASSESSMENT OF THE RELATIVE TOXICITY OF CANDIDATE INSECT REPELLENTS

AI3-36465	AI3-54169
AI3-37410	AI3-54170
AI3-37414	AI3-20698
AI3-37416	AI3-38142
AI3-37577	AI3-39672
AI3-38661	

U.S. DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS STUDY NOS.

75-51-0797-92	75-51-0803-92
75-51-0798-92	75-51-0804-92
75-51-0799-92	75-51-0828-92
75-51-0800-92	75-51-0829-92
75-51-0801-92	75-51-0830-92
75-51-0802-92	

APRIL 1992

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Since 1942, USAEHA has provided worldwide preventive medicine support to the Army, Department of Defense and other Federal agencies. The USAEHA accomplishes this mission by providing information and consultative services to leaders and decision makers charged with the responsibility for the occupational and environmental health of military and civilian service members and associated communities worldwide. The USAEHA is unique nationally in its ability to matrix and tailor its staff, representing a wide array of scientific disciplines, for immediate response to occupational and environmental health crises and issues.

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

EXECUTIVE SUMMARY
TOPICAL HAZARD EVALUATION PROGRAM, ASSESSMENT OF THE RELATIVE TOXICITY OF CANDIDATE INSECT REPELLENTS

AI3-36465	AI3-54169
AI3-37410	AI3-54170
AI3-37414	AI3-20698
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AI3-38661	

U.S. DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS STUDY NOS.

75-51-0797-92	75-51-0803-92
75-51-0798-92	75-51-0804-92
75-51-0799-92	75-51-0828-92
75-51-0800-92	75-51-0829-92
75-51-0801-92	75-51-0830-92
75-51-0802-92	

APRIL 1992

1. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of candidate insect repellents; U.S. Department of Agriculture proprietary chemicals.

2. RECOMMENDATIONS.

a. Approve candidate insect repellents AI3-36465, AI3-37410, AI3-37416, AI3-37577, AI3-38661, AI3-54169, AI3-54170, AI3-20698, AI3-38142, and AI3-39672 for further testing.

b. Conduct no further entomological studies on candidate repellent AI3-37414 due to its demonstrated potential for causing primary skin irritation.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T

TOPICAL HAZARD EVALUATION PROGRAM, ASSESSMENT OF THE RELATIVE TOXICITY OF CANDIDATE INSECT REPELLENTS

AI3-36465	AI3-54169
AI3-37410	AI3-54170
AI3-37414	AI3-20698
AI3-37416	AI3-38142
AI3-37577	AI3-39672
AI3-38661	

U.S. DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS STUDY NOS.

75-51-0797-92	75-51-0803-92
75-51-0798-92	75-51-0804-92
75-51-0799-92	75-51-0828-92
75-51-0800-92	75-51-0829-92
75-51-0801-92	75-51-0830-92
75-51-0802-92	

APRIL 1992

1. REFERENCES.

a. Toxicology Division, Topical Hazard Evaluation Program Procedural Guide, October 1985.

(1) Standing Operating Procedure (SOP) No. 8, U.S. Army Environmental Hygiene Agency (USAEHA), HSHB-MO-T, Primary Dermal Irritation Study.

(2) SOP No. 7, USAEHA, HSHB-MO-T, Primary Eye Irritation Study.

(3) SOP No. 12, USAEHA, HSHB-MO-T, Photochemical Skin Irritation Study.

(4) SOP No. 61, USAEHA, HSHB-MO-T, Guinea Pig Skin Sensitization Test (Buehler Technique).

Use of trademarked names does not imply endorsement by the U.S. Army but is intended only to assist in identification of a specific product.

Tox Eval Nos. 75-51-0797 through 0804, and 0828 through 0830-92, Apr 92

b. Toxicity of Arthropod Repellents, Appraisal of the Armed Forces Topical Hazard Evaluation Program (THEP). Subcommittee on Arthropod Repellents, Committee on Toxicology, National Research Council. National Academy Press, Washington, DC, 1987.

2. AUTHORITY.

a. Letter, U.S. Department of Agriculture, Agricultural Research Service, Northeastern Region, Beltsville, Agricultural Research Service, Beltsville, Maryland, 3 Sep 86, subject: Chemical Transmittal for THEP.

b. Memorandum of Understanding between the U.S. Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Management Board; and the U.S. Department of Agriculture, Agricultural Research, titled Biological and Toxicological Testing of Pesticides, effective 7 October 1987.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of candidate insect repellents; U.S. Department of Agriculture (USDA) proprietary chemicals.

4. MATERIALS.

a. Test Compounds. The eleven candidate insect repellents used in these studies were synthesized and provided by the Insect Chemical Ecology Laboratory, Agriculture Research Service, USDA, Beltsville, Maryland.

b. Animals.*†

(1) Testing for primary skin irritation, photochemical skin irritation, and primary eye irritation was conducted using New Zealand White rabbits (2.8-4.5 kg) of either sex obtained from Hazelton-Dutchland Laboratories, Denver, Pennsylvania. Female Albino-Hartley guinea pigs (375-425 gm), also from Hazelton-Dutchland Laboratories, were used for sensitization

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* In conducting the studies described herein, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," U.S. Department of Health, Education and Welfare Publication No. (NIH) 85-23, 1985.

† The studies reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

studies and for determination of dermal toxicity. Male Sprague-Dawley rats (175-225 gm) from Charles River Laboratories, Wilmington, Massachusetts, were used for the oral toxicity studies. Quality control determinations made during a 2-week quarantine period showed the animals to be of acceptable health.

(2) Rabbits, guinea pigs and rats were housed individually in wire-bottom stainless steel cages. Drinking quality water and feed (Purina® Rabbit Chow 5322; Ziegler Rodent Ration 35-553 and Ziegler Certified Guinea Pig ration 35-564) were available ad libitum. Ambient temperatures in the animal rooms were maintained at 21 to 25 °C with relative humidity between 40-60 percent. The light/dark cycle was 12-hour intervals.

c. Contract Studies. Mutagenicity evaluation of the test substances was performed under commercial contract by Integrated Laboratory Systems, Research Triangle Park, North Carolina. The contract numbers were DAAD05-90P-0770 and DAAD05-91P-0170.

5. METHODS.

a. Skin Irritation. An acute dermal irritation test, based upon the method of Draize, was conducted in rabbits. The procedure [reference 1a(1)] involved the single application of 0.5 gm or mL of each test substance to the clipped backs of six rabbits. The materials were held in contact with the skin under a gauze patch and overwrap of Coban® (occlusive). Exposure was for 24 hours following by scoring of irritation. Evaluations were also performed at 48 and 72 hours and at 7 days. Scoring of irritation was based on the Draize method in which erythema and edema were evaluated on a scale of 0 to 4 for severity. Categorizing the responses was based on the mean of the sum of the 24- and 48-hour scores.

b. Eye Irritation. Eye irritation studies were performed in rabbits following a standard method [reference 1a(2)]. A single 0.1 gm or mL dose of the test substance was administered to the conjunctival sac of each of six rabbits. Eyes were examined for gross signs of irritation at 24, 48, and 72 hours, and 7 days following exposure. Scoring of irritation effects followed the

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® Coban is a registered trademark of the Minnesota, Mining and Manufacturing Co., St. Paul, Minnesota.

method of Draize in which the total score for the eye is the sum of all scores obtained for the cornea, iris, and conjunctiva. Categorizing the responses was based on the 24-hour evaluation.

c. Photochemical Skin Irritation. A photochemical skin irritation study was performed to assess the potential of the test substances to become chemically reactive when exposed to sunlight. Studies were performed [reference 1a(3)] by applying 0.05 mL of the test solution (25 percent in 95 percent ethanol) to the right side of the clipped backs of six rabbits. After 5 minutes the backs were exposed to ultraviolet (UV) light (365 nm) for 30 minutes at a distance of 10-15 cm. Following UV exposure of the rabbits, the left side of the same animal's back was treated identically to the right side, except that it was not irradiated. Oil of Bergamot, a known photoirritant, was included in the exposure regimen to assure the responsiveness of the test system. Photochemical irritation was evaluated at 24, 48, and 72 hours post-exposure. Scoring of erythema and edema was based upon the method of Draize.

d. Dermal Toxicity. An approximate lethal dose (ALD) was performed in guinea pigs to determine the dermal toxicity of the subject chemicals. Single graded doses of the technical grade material were injected under an occlusive rubber sleeve which surrounded the clipped trunk of each animal. The sleeve was removed after 24 hours. Animals were examined daily for toxic signs through 14 days. Survivors were euthanized at day 14 and examined grossly for pathology. The ALD of the test substance was considered the lowest dose that caused death during the 14-day observation period.

e. Oral Toxicity - ALD. An ALD study, which uses a small number of animals, was performed to determine the minimum lethal dose of the test chemical. Single oral graded doses of technical grade material were given by gavage to male rats. Following administration of the test substance, animals were examined daily for the onset of toxic signs. Animals surviving the 14-day observation period were sacrificed for gross pathological examination. The ALD of the test substance was considered the lowest dose that caused death during the 14-day observation period.

f. Skin Sensitization. Sensitization studies were performed to determine the potential of the test substance for causing skin sensitization reactions in humans. The test procedure was based on the method of Buehler [reference 1a(4)]. Technical grade test

material was applied under Webril® patches to the shaved backs of 10 guinea pigs. Dinitrochlorobenzene, a known skin sensitizer, was included as a positive control. The occlusive exposure was for 6 hours, once per week, for 3 weeks. This was considered the "induction" phase. Following a 2-week rest period the animals were "challenged," meaning that a single application of the test material was applied to a naive site. Five additional naive animals also received the challenge dose. Twenty-four and 48 hours after the challenge, the skin was depilated then irritation scored 3 hours later. The appearance of erythema and/or edema at the challenge site which was greater than that observed on the naive animals (no induction) was considered an allergic response.

g. In Vitro Mutagenicity Assays. The subject chemicals were evaluated for mutagenic activity in the Ames Salmonella/Microsome Plate assay. The Ames test used Salmonella typhimurium indicator strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100. The assays were conducted in duplicate and in the presence of metabolic activation. The assays were conducted at doses based on preliminary toxicity tests with the strain TA-100. For the actual assay, doses were selected with the highest dose exhibiting ≤ 90 percent toxicity and ranged over a series of five doses, from 5 µL/plate to 50 µL/plate.

6. RESULTS.

a. Skin Irritation. A tabular presentation of the skin irritation data for each test substance appears at Table 1.

b. Eye Irritation. A tabular presentation of the eye irritation data appears at Table 2.

c. Photochemical Irritation. A tabular presentation of the photochemical irritation data appears at Table 3.

d. Dermal Toxicity. A tabular presentation of the dermal toxicity data appears at Table 4.

e. Oral Toxicity - ALD. A tabular presentation of the oral toxicity data appears at Table 5.

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Tox Eval Nos. 75-51-0797 through 0804, and 0828 through 0830-92, Apr 92

TABLE 1. SKIN IRRITATION

Substance	Study No.	Results	Category* USAEHA	Category* EPA
AI3-36465	75-51-0797-92	Slight irritation with scores from 1 to 0 with a mode of 0.	I	IV
AI3-37410	75-51-0798-92	Slight irritation with scores from 1 to 0 with a mode of 0.	I	IV
AI3-37414	75-51-0799-92	Moderate irritation with scores from 3 to 0 with a mode of 0. Unresolved by day 7.	III	III
AI3-37416	75-51-0800-92	Moderate irritation with scores from 2 to 0 with a mode of 0.	II	III
AI3-37577	75-51-0801-92	Moderate irritation with scores from 2 to 0 with a mode of 0.	II	III
AI3-38661	75-51-0802-92	Slight irritation with scores from 1 to 0 with a mode of 0.	I	IV
AI3-54169	75-51-0803-92	Mild irritation with scores from 2 to 0 with a mode of 0.	II	IV
AI3-54170	75-51-0804-92	Moderate irritation with scores from 2 to 0 with a mode of 0.	II	III
AI3-20698	75-51-0828-92	Mild irritation with scores from 2 to 0 with a mode of 0.	II	IV
AI3-38142	75-51-0829-92	Mild irritation with scores from 2 to 0 with a mode of 0.	II	IV
AI3-39672	75-51-0830-92	Mild irritation with scores from 2 to 0 with a mode of 0.	II	IV

* See Appendix A for USAEHA Categories and Appendix B for EPA Categories.

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TABLE 2. EYE IRRITATION

Substance	Study No.	Results	Category* USAEHA	Category* EPA
AI3-36465	75-51-0797-92	Slight corneal opacity.	A	III
AI3-37410	75-51-0798-92	Moderate corneal opacity with iritis and moderate conjunctival irritation. Resolved by day 7.	E	III
AI3-37414	75-51-0799-92	Mild corneal opacity with iritis and moderate conjunctival irritation. Resolved in 7 days.	C	III
AI3-37416	75-51-0800-92	Mild corneal opacity and moderate conjunctival irritation. Cleared by 72 hours.	C	III
AI3-37577	75-51-0801-92	Mild corneal opacity with iritis and moderate conjunctival irritation. Resolved by day 7.	C	III
AI3-38661	75-51-0802-92	Moderate corneal opacity with iritis and moderate conjunctival irritation. Resolved by 14 days.	E	II
AI3-54169	75-51-0803-92	Slight corneal opacity and slight conjunctival irritation.	A	III
AI3-54170	75-51-0804-92	No effects on the eye.	A	IV
AI3-20698	75-51-0828-92	Mild to moderate corneal opacity and irritation to the conjunctiva. Cleared by 7 days.	C	III
AI3-38142	75-51-0829-92	Moderate corneal opacity and moderate conjunctival irritation. Cleared by 7 days.	E	III
AI3-39672	75-51-0830-92	Slight corneal opacity and conjunctival irritation.	A	III

* See Appendix C for USAEHA Categories and Appendix B for EPA Categories.

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TABLE 3. PHOTOCHEMICAL IRRITATION

Substance	Study No.	Results
AI3-36465	75-51-0797-92	No photochemical irritation.
AI3-37410	75-51-0798-92	No photochemical irritation.
AI3-37414	75-51-0799-92	No photochemical irritation.
AI3-37416	75-51-0800-92	No photochemical irritation.
AI3-37577	75-51-0801-92	No photochemical irritation.
AI3-38661	75-51-0802-92	No photochemical irritation.
AI3-54169	75-51-0803-92	No photochemical irritation.
AI3-54170	75-51-0804-92	No photochemical irritation.
AI3-20698	75-51-0828-92	No photochemical irritation.
AI3-38142	75-51-0829-92	No photochemical irritation.
AI3-39672	75-51-0830-92	No photochemical irritation.

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TABLE 4. DERMAL TOXICITY - ALD

Substance	Study No.	Approximate Lethal Dose		EPA Category*
AI3-36465	75-51-0797-92	>3333 mg/kg.	No signs.	III
AI3-37410	75-51-0798-92	>3333 mg/kg.	No signs.	III
AI3-37414	75-51-0799-92	Not performed.		III
AI3-37416	75-51-0800-92	>3333 mg/kg.	No signs.	III
AI3-37577	75-51-0801-92	>3333 mg/kg.	No signs.	III
AI3-38661	75-51-0802-92	>3333 mg/kg.	No signs.	III
AI3-54169	75-51-0803-92	>3333 mg/kg.	No signs.	III
AI3-54170	75-51-0804-92	>3333 mg/kg.	No signs.	III
AI3-20698	75-51-0828-92	>3333 mg/kg.	No signs.	III
AI3-38142	75-51-0829-92	>3333 mg/kg.	No signs.	III
AI3-39672	75-51-0830-92	>3333 mg/kg.	No signs.	III

* See Appendix B for EPA Categories.

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TABLE 5. ORAL TOXICITY - ALD

Substance	Study No.	Approximate Lethal Dose	Signs	EPA Category*
AI3-36465	75-51-0797-92	>3333 mg/kg	Lethargy; red exudate-muzzle area.	III
AI3-37410	75-51-0798-92	>3333 mg/kg	Salivation.	III
AI3-37414	75-51-0799-92	>3333 mg/kg	Salivation.	III
AI3-37416	75-51-0800-92	>3333 mg/kg	Ataxia.	III
AI3-37577	75-51-0801-92	>3333 mg/kg	No signs.	III
AI3-38661	75-51-0802-92	>3333 mg/kg	Salivation; ataxia; prostration.	III
AI3-54169	75-51-0803-92	>3333 mg/kg	No compound-related signs.	III
AI3-54170	75-51-0804-92	>3333 mg/kg	No signs.	III
AI3-20698	75-51-0828-92	>3333 mg/kg	Hemolachrymation; red exudate-muzzle area.	III
AI3-38142	75-51-0829-92	>3333 mg/kg	Salivation; gasping; hemo-lachrymation.	III
AI3-39672	75-51-0830-92	>3333 mg/kg	Salivation; ataxia; hemo-lachrymation.	III

* See Appendix B for EPA Categories.

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f. Skin Sensitization. A tabular presentation of the skin sensitization data appears at Table 6.

g. Mutagenicity. The Ames test results appear at Table 7.

7. DISCUSSION.

a. The purpose of the Topical Hazard Evaluation Program is to investigate relevant health endpoints of proposed repellent chemicals. Data from these studies are used to recommend the course of further entomological and toxicological evaluations with the subject chemicals.

b. The results from the acute skin irritation studies showed that one of the test compounds, AI3-37414, caused significant skin irritation. The material was classified USAEHA, Category III which is a basis for rejecting a material as a topical insect repellent.

c. The results of the eye irritation tests showed that three compounds produced significant irritation resulting in a USAEHA, Category E classification. This finding, however, is no longer considered a basis for rejecting a candidate repellent without comparative studies with diethyl-m-toluamide at equally efficacious doses (reference 1b). Further eye irritation testing is indicated with the three candidate repellents if their development progresses to Step 5, Advanced Toxicology, Part 1.

d. The results of the Ames tests for mutagenicity showed only intermittent positive responses for 9 of the 11 compounds tested. The responses were generally weak and were not consistent among the five indicator strains used. It must be noted that the Ames test considers only one endpoint (gene mutation) whereas a battery of in vitro assays, looking at several different endpoints, are needed to accurately predict the mutagenic potential of a substance. Additional mutagenicity assays will be performed on candidate repellents progressing to Step 5.

8. RECOMMENDATIONS.

a. Approve candidate repellents AI3-36465, AI3-37410, AI3-37416, AI3-37577, AI3-38661, AI3-54169, AI3-54170, AI3-20698, AI3-38142, and AI3-39672 for additional entomological testing.

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TABLE 6. SKIN SENSITIZATION

Substance	Study No.	Results
AI3-36465	75-51-0797-92	No sensitization reaction.
AI3-37410	75-51-0798-92	No sensitization reaction.
AI3-37414	75-51-0799-92	No sensitization reaction.
AI3-37416	75-51-0800-92	No sensitization reaction.
AI3-37577	75-51-0801-92	No sensitization reaction.
AI3-38661	75-51-0802-92	No sensitization reaction.
AI3-54169	75-51-0803-92	No sensitization reaction.
AI3-54170	75-51-0804-92	No sensitization reaction.
AI3-20698	75-51-0828-92	No sensitization reaction.
AI3-38142	75-51-0829-92	No sensitization reaction.
AI3-39672	75-51-0830-92	No sensitization reaction.

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TABLE 7. MUTAGENICITY - AMES TEST

Substance	Study No.		Indicator Strains TA1535	TA1537	TA1538	TA98	TA100
AI3-36465	75-51-0799-92	Act	-	+	-	-	-
		Nonact	-	-	-	-	-
AI3-37410	75-51-0798-92	Act	-	-	-	(w)+	-
		Nonact	-	-	-	-	-
AI3-37414	75-51-0799-92	Act	Not performed.				
		Nonact	Not performed.				
AI3-37416	75-51-0800-92	Act	-	(w)+	-	-	-
		Nonact	-	(w)+	-	-	-
AI3-37577	75-51-0801-92	Act	-	-	-	-	-
		Nonact	-	+	-	-	-
AI3-38661	75-51-0802-92	Act	-	-	-	-	-
		Nonact	-	(w)+	-	-	-
AI3-54169	75-51-0803-92	Act	-	-	-	-	-
		Nonact		-	-	-	-
AI3-54170	75-51-0804-92	Act	+	-	-	-	+
		Nonact	-	-	-	-	+
AI3-20698	75-51-0828-92	Act	-	(w)+	-	-	-
		Nonact	(w)+	-	-	-	-
AI3-38142	75-51-0829-92	Act	-	-	-	-	-
		Nonact	-	-	-	-	-
AI3-39672	75-51-0830-92	Act	-	-	-	-	-
		Nonact	-	-	-	(w)+	(w)+

KEY:
Positive response (+)
Negative response (-)
Activated (Act)
Nonactivated (Nonact)
Weak (w)

b. Disapprove candidate repellent AI3-37414 for further entomological testing based upon its demonstrated skin irritancy.

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APPROVED:

MAURICE H. WEEKS
Chief, Toxicology Division

Tox Eval Nos. 75-51-0797 through 0804, and 0828 through 0830-92, Apr 92

APPENDIX A

USAEHA CATEGORIES FOR SKIN IRRITATION EFFECTS

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. Score Limits: Intact 0-0.5; Abraded 0.51-2.0; Total 0-2.0 (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. Score Limits: Intact >0.5; Total 0.51-2.0 (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. Score Limits: Total 2.1-5.0 (INTERPRETATION: Should not be used directly without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion. Score Limits: Total 2.1-7.9 (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound or compounds producing necrosis, vesiculation, or eschars. Score Limits: Total 8.0 or not scorable. (INTERPRETATION: Not suitable for use on humans.)

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APPENDIX B

EPA - TOXICITY CATEGORY CRITERIA

Hazard Indicators	Category I	Category II	Category III	Category IV
Oral LD50	Up to and incl 50 mg/kg	>50 thru 500 mg/kg	>500 thru 5000 mg/kg	>5000 mg/kg
Dermal LD50	Up to and incl 200 mg/kg	>200 thru 2000 mg/kg	>2000 thru 20,000 mg/kg	>20,000 mg/kg
Inhal LC50 (Chmbr conc)	Up to and incl 0.2 mg/L	<0.2 thru 2.0 mg/L	>2.0 thru 20 mg/L	>20 mg/L
Eye Effects	Corrosive (Irrevers de-struc of ocular tiss) or corneal involv or irrit persist for more than 21 days	Corneal involv or irrit clrng in 8-21 days	Corneal involv or irrit clrng in 7 days or less	Min effects clrng in less than 24 hrs
Skin Effects	Corrosive (Tiss destruc into dermis and/or scarring)	Sev irrit at 72 hrs (sev erythema or edema)	Mod irrit at 72 hrs (mod erythema)	Mild or slt irrit (no irrit or slt erythema)

References:

40 CFR 156.10, Labeling Requirements, revised 1 July 1990.

Eye Effects: [EPA] PR Notice 81-3; Label Improvement Program: Change in Test Methods for and Categorization of Eye Irritation, 29 September 1981.

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APPENDIX C

USAEHA CATEGORIES FOR EYE IRRITATION EFFECTS

CATEGORY A - Compounds noninjurious to the eye. Score Limits: 0-10 (individual conjunctival score for chemosis, redness or discharge not to exceed 1). (INTERPRETATION: Irritation of human eyes is not expected if the compound should accidently get into the eyes, provided it is washed out as soon as possible.)

CATEGORY B - Compounds producing mild injury to the cornea. Score Limits: 10-20 (individual conjunctival score for chemosis, redness or discharge not to exceed 1). (INTERPRETATION: To be used with caution around the eyes.)

CATEGORY C - Compounds producing mild injury to the cornea, and in addition, some injury to the conjunctiva. Score Limits: 5-30 (individual conjunctival score for chemosis, redness or discharge exceed 1). [INTERPRETATION: To be used with caution around the eyes and mucosa (e.g., nose and mouth).]

CATEGORY D - Compounds producing moderate injury to the cornea. Score Limits: <20-50 (individual conjunctival score for chemosis, redness or discharge not to exceed 1). (INTERPRETATION: To be used with extreme caution around the eyes.)

CATEGORY E - Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. Score Limits: 20-50 (individual conjunctival score for chemosis, redness or discharge exceed 1). (INTERPRETATION: To be used with extreme caution around the eyes and mucosa.)

CATEGORY F - Compounds producing severe injury to the cornea and to the conjunctiva. Sore Limits: 50 or greater. (INTERPRETATION: To be used only with extreme caution; it is recommended that use be restricted to areas other than the face.)

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APPENDIX D

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following with regard to this study:

a. This study was conducted in accordance with:

(1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.

(2) Title 21, Code of Federal Regulations (CFR), 1991 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

b. Facilities were inspected during its operational phase to ensure compliance with paragraph a above. Dates of inspection were:

1, 6, and 7 February 1990	11 April 1990
6 and 14 March 1990	3, 8, 15, 16, and 17 May 1990

c. The information presented in this report accurately reflects the raw data generated during the course of conducting the study.

TIMOTHY L. FISHER
Chief, Analytical Quality
Assurance Division